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(54) **Aza macrocycles and processes for their preparation**

Aza-Macrozykien und Verfahren zu deren Herstellung

Azamacrocycles et procédé pour leur préparation

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- **CHEMICAL ABSTRACTS, vol. 109, no. 18, October 31, 1988, Columbus, Ohio, USA; FUKUDA Y. et al.: "1,4,7-triazacyclononane-N,N',N"-trialkanoic acids-metal complexes and electrochromic elements using them", page 765, column 1, abstract-no. 160 661p & Jpn. Kokai Tokkyo Koho JP 62,298,578 (87,298,578)**

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Description

Field of the Invention

This invention relates to functionalised aza macrocycles, to metal complexes thereof, to conjugate compounds containing the functionalised aza macrocycles and metal complexes thereof and to their use in diagnosis and therapy.

Background to the Invention

The attachment of metal ions to proteins, peptides and other, smaller molecules is a fast expanding technology, which has numerous proven and potential applications in research, in industry and, particularly, in medicine.

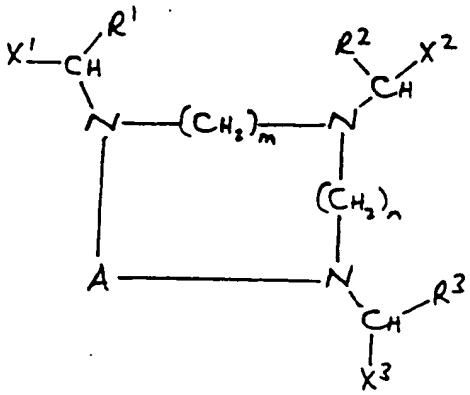
In recent years, much of the impetus behind the development of this technology has been the ability to link metal ions to antibodies, especially monoclonal antibodies. Such metal labelled antibodies have found a widespread use, especially in medicine, where they have been employed, for example, to target the metal ion to a specific tissue type, both in vitro and in vivo. Thus, metal labelled antibodies have applications in locating specific tissue types (e.g. employing computer-aided tomographic techniques where the metal ion is in some way detectable) and in the treatment of cell disorders (e.g. treating mammalian tumours where the metal ion is a cytotoxic radionuclide).

Conventionally, attachment of the metal ion to a protein such as an antibody has been achieved by complexation by an acyclic chelate such as a substituted diethylenetriaminepentaacetic acid [Gansow O. A. et al, Inorg. Chem., (1986), 25, 2772] or ethylenediaminetetraacetic acid [Meares, C. F. et al, Acc. Chem. Res., (1984), 17, 202] covalently linked to the antibody. Such acyclic complexes however tend to be unstable in vivo either as a result of acid-catalysed decomplexation or competitive chelate binding by Ca^{2+} or Zn^{2+} in serum, or as a result of competition from transferrin [Moerlein, S. M. et al, Int. J. Nuc. Med. Biol., (1981) 8, 277]. The lack of stability can result in uncomplexed metal atoms in the body which have a cytotoxic effect on healthy tissue (e.g. bone marrow) or which markedly reduce the signal-to-noise ratio of an imaging technique.

A possible alternative to the use of acyclic chelates in the labelling of antibodies is the use of macrocyclic ligands, which has been suggested by a number of workers [Gansow O. A. et al. Am. Chem. Soc. Symp. Ser., (1984), 241, 215; UK Patent Specification Publication No. 2122641; International Patent Specifications Nos. WO89/01475 and WO89/01476 and European Patent Specification No. 305320; and Moi M. K. et al, Anal. Biochem., (1985), 148, 249-253].

We have now found a new class of functionalised aza macrocycles, members of which are able to form kinetically inert complexes with metal ions. The macrocycles of the invention are particularly useful for attachment to proteins, especially antibodies, to provide conjugate compounds capable of binding metals to give complexes which are advantageously stable in vivo.

Thus, according to one aspect of the present invention we provide a compound of general formula (1);



(1)

wherein

A is a group $-(CH_2)_p-$ or $-(CH_2)_p N(R)(CH_2)_q-$ where R is a group $-CH(R^4)X^4$;

m, n, p, and q is each an integer 2;

R^1, R^2, R^3 and R^4, which may be the same or different, is each a group $-CO_2H$, $-P(R^5)O_2H$ (where R^5 is a hydrogen atom or a C_{1-6} alkyl or alkoxy group), $-PO_3H_2$ or $-CONR^6R^7$ (where R^6 and R^7, which may be the same or different is each a hydrogen atom or a C_{1-6} alkyl group);

X^1, X^2, X^3 and X^4, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group, or a linker group of the formula -L-Z wherein L and Z are as defined below, with the proviso that at least one of X^1, X^2, X^3 or X^4 is a linker group; and metal complexes and/or salts thereof.

It will be appreciated that formula (1) [and, where appropriate, the following formulae herein], is intended to cover all stereoisomers of the compounds concerned, including mixtures thereof.

In the compounds of formula (1), it will be appreciated that the nature of the linker group may be varied widely without substantially affecting the usefulness of the compounds.

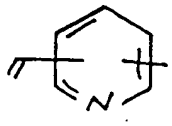
In the following definition, and in the same context whenever it appears below, the term "interrupted by" as applied to cycloaliphatic or aromatic groups is to be understood to also mean that these particular groups may additionally be present linked to the terminal carbon atom of the hydrocarbyl chain represented by L, at the opposite end of the chain to the carbon atom attached to the macrocycle.

L is an optionally substituted straight or branched C_{1-20}alkylene, C_{2-20}alkenylene, or C_{2-20}alkynylene chain, optionally interrupted by one or more -O- or -S- atoms or C_{5-8}cycloalkylene (e.g. cyclopentylene or cyclohexylene), C_{6-12}aromatic (e.g. phenylene or substituted phenylene), C_{5-10}heteroaromatic (e.g. furanyl, pyridyl), -N(R^8)-, -CON(R^8)- or -N(R^8)CO- groups (where R^8 is a hydrogen atom or a C_{1-6} alkyl group).

Examples of substituents which may be present on the chain L include halogen atoms, e.g. fluorine, chlorine, bromine, or iodine atoms or groups selected from C_{1-6}alkoxy (e.g. methoxy or ethoxy), hydroxy, nitro, -N(R^9)(R^{10}), [where R^9 is a hydrogen atom or a C_{1-6}alkyl group and R^{10} is a C_{1-6}alkyl group; e.g. -$NHCH_3$ or -$N(CH_3)_2$], or substituted amido, e.g. a group of formula -$(CH_2)_d$CON(R^{11})(R^{12}) [where d is zero or an integer 1 to 4 inclusive, R^{11} is a hydrogen atom or a C_{1-6}alkyl group, e.g. methyl and R^{12} is an optionally substituted C_{1-6}alkyl group].

Substituted alkyl groups represented by R^{11} include for example C_{1-6}alkyl groups substituted by one or more halogen atoms, or nitro, amino or hydroxy groups.

Z is a halogen atom, for example a chlorine, bromine or iodine atom, or a group selected from OH, -SH, -NH_2, hydrazine (-$NHNH_2$), or a derivative thereof, [for example -$N(CH_3)NH_2$, -NHCONHNH_2, -NHCSNHNH_2, or phenyl hydrazine], -NCO, -NCS, -COR^{13}, [where R^{13} is a halogen atom such as a chlorine or bromine atom, or a N_3, C_{1-6}alkoxy, e.g. methoxy, C_{6-12}aryloxy (e.g. nitrophenyloxy or dinitrophenyloxy), imidyloxy (e.g. succinimidyloxy) or imidazolyloxy group], imide,e.g. maleimide, a vinyl group of formula -Het^1-C(Het^2)=CH_2 (where Het^1 and Het^2, which may be the same or different, is each a nitrogen containing heterocyclic group, e.g. a pyridyl group or Het^1 is a nitrogen containing heterocyclic group and Het^2 is a hydrogen atom), for example a vinyl pyridyl group of formula



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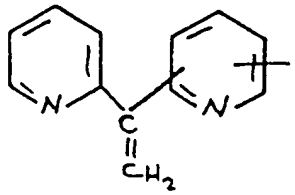

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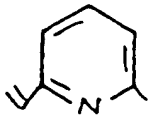

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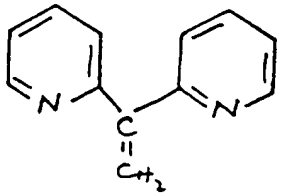

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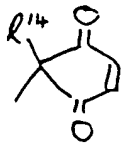


(where R^{14} is a C_{1-4}alkyl e.g. methyl group).

Alkyl groups represented by the groups X^1, X^2, X^3, X^4, R^5, R^6 or R^7 include C_{1-6}alkyl groups such as methyl or ethyl groups.

Metal complexes of the compounds of formula (1) in which A is $-(CH_2)_pN(R)(CH_2)_q-$ include complexes wherein the metal is di- or tripositive and has a coordination number 6 or greater, especially 8. Examples of such metals include indium (In), copper (Cu), lead (Pb), bismuth (Bi), yttrium (Y), terbium (Tb), gallium (Ga), gadolinium (Gd) and scandium (Sc). In, Y, Ga, Tb, Gd, and Sc are preferred, particularly In, Y, Gd, and Ga. In general the metal is preferably a radioactive isotope. Yttrium, especially ^{90}Y, is particularly preferred.

Metal complexes of the compounds of formula (1) in which A is $-(CH_2)_p-$ include complexes wherein the metal is di- or tri-positive and has a coordination number from 2 up to 6, especially 6. Examples of such metal(s) include indium (In), copper (Cu), lead (Pb), bismuth (Bi), cobalt (Co) and gallium (Ga). In, Ga, Co and Cu are preferred, particularly In and Ga. In general the metal is preferably a radioactive isotope. Indium, especially ^{111}In, is particularly preferred.

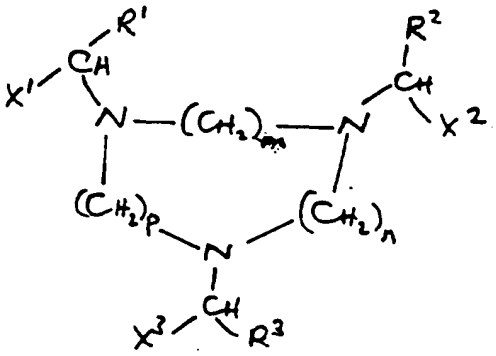
In general, optimum binding of the metal to the compounds of formula (1) may be achieved by selection of the ring size and where appropriate by adjusting the potential coordination number by choice of the group R^1, R^2, R^3 or R^4.

Salts of the compounds of formula (1) include salts with bases, e.g. sodium or potassium salts, or acid addition salts such as hydrobromides or hydrochlorides. Pharmaceutically acceptable salts are particularly preferred.

A preferred group of compounds of formula (1) wherein A is $-(CH_2)_p-$ or $-(CH_2)_pN(R)(CH_2)_q-$ is that wherein R^1, R^2, R^3, and R^4 is each a $-CO_2H$ group.

A further preferred group of compounds of formula (1) wherein A is $-(CH_2)_p-$ or $-(CH_2)_pN(R)(CH_2)_q-$ is that wherein one or two of X^1, X^2, X^3 and X^4 is a linker group and the remainder are alkyl groups or, especially, hydrogen atoms.

One group of compounds of formula (1) has the formula (1a):

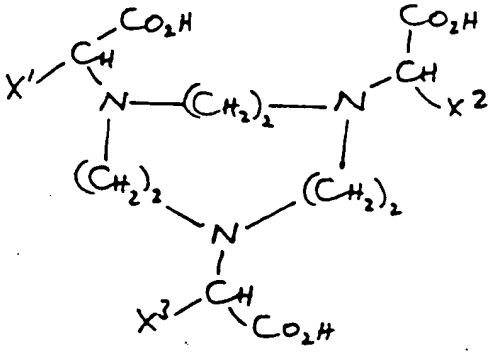


(1a)

wherein m, n, p, R^1, R^2, R^3, X^1, X^2 and X^3 are as defined for formula (1); and metal complexes and/or salts thereof.

Indium complexes of the compounds of formula (1a) are particularly preferred.

Particularly important compounds of formula (1a) are those of formula (1b)

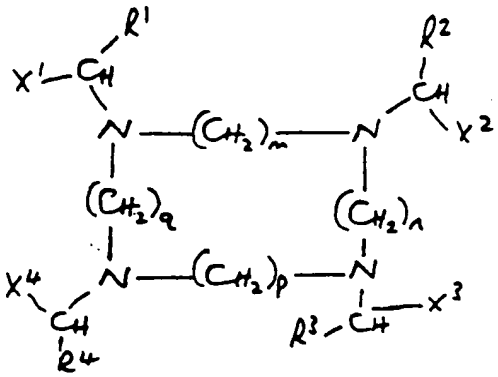


(1b)

wherein one or two of X^1, X^2, or X^3 is a linker group and the remainder are hydrogen atoms; and metal complexes and/or salts thereof.

Indium complexes of the compounds of formula (1b) are particularly preferred.

Another group of compounds of formula (1) has the formula (1c):

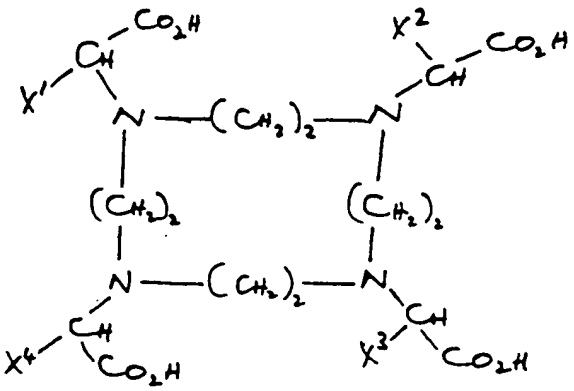


(1c)

wherein m, n, p, q, R^1, R^2, R^3, R^4, X^1, X^2, X^3 and X^4 are as defined for formula (1); and metal complexes and/or salts thereof.

Yttrium complexes of the compounds of formula (1c) are particularly preferred.

An important group of compounds of formula (1c) are those of formula (1d)



(1d)

wherein one or two of X^1, X^2, X^3 or X^4 is a linker group and the remainder are hydrogen atoms; and metal complexes and/or salts thereof.

Yttrium complexes of the compounds of formula (1d) are particularly preferred.

The compounds of formula (1) and the metal complexes and/or salts thereof have a diagnostic use as imaging agents in vitro and in vivo. The compounds of formula (1) and the metal complexes and/or salts thereof are also cytotoxic agents and may be used in the treatment of abnormal cell disorders, for example in the treatment of tumours. For use as diagnostic and/or therapeutic agents, the compounds of formula (1) may be employed using conventional methods, (e.g. for formulation and presentation) already in use for metal complexing agents.

For application of the compounds of formula (1) as imaging or cytotoxic agents, it is generally preferable to couple the compounds to other molecules such a proteins, especially antibodies, peptides or carbohydrates to form conjugate compounds, and the compounds of formula (1) are particularly well adapted for use in this respet.

Thus, according to a further aspect of the invention, we provide a conjugate compound which comprises a compound of formula (1), or a metal complex and/or salt thereof, coupled to a protein, peptide or carbohydrate.

The compound of formula (1) may be coupled through any thiol, amino, carboxyl, hydroxyl, aldehyde, aromatic or heteroaromatic group present in the protein, peptide or carbohydrate.

In a preferred aspect of the invention, we provide a conjugate compound which comprises a compound of formula (1) or a metal complex and/or salt thereof, coupled to an antibody.

It is to be understood that conjugate compounds according to the invention may contain more than one molecule of a compound of formula (1) couple to any one protein, peptide or carbohydrate molecule.

Particularly useful conjugate compounds according to the invention are those comprising a compound of formula (1b) or formula (1d) or a metal complex and/or salt thereof, coupled to an antibody. The indium and yttrium complexes of these conjugates are especially important.

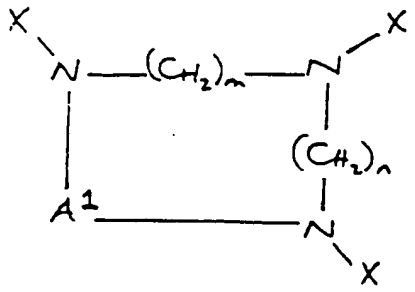
The compounds of formula (1) and conjugate compounds of the invention may be formulated for use in accordance with conventional practice. Thus according to a further aspect of the invention we provide a composition comprising a compound of formula (1); or a conjugate compound comprising a compound of formula (1) coupled to a protein, peptide or carbohydrate, or a metal complex and/or salt thereof, together with one or more pharmaceutically acceptable carriers.

Particularly suitable compositions according to the invention are those adapted for parenteral administration, especially by injection or infusion. Suitable formulations of this type include suspensions solutions or emulsions of the compound or conjugate in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the compound or conjugate may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water before use. If desired the compound or conjugate may be presented in unit dosage form, and/or together with one or more active ingredients or imaging agents. Suitable formulations of this type include solutions of the compounds of formula (1) in isotonic saline.

The quantities of compounds of formula (1) used in formulations according to the invention will vary according to the intended cell target, but may be easily determined in accordance with conventional practice for reagents of this type.

Compounds of the invention may be prepared by the following processes wherein the groups and symbols R^1, R^2, R^3, R^4, m, n, p, q, X^1, X^2, X^3 and X^4 are as defined for formula (1) except where stated otherwise. Where a metal complex is desired as a final product, the complexation with a metal atom may be carried out as a final step in the production process, as described below for the complexation of compounds of formulae (1), or alternatively it may be desirable to complex the metal at an earlier stage in the process, providing of course that the requisite macrocycle structure is present. In the following processes, it may be desirable to use starting materials in which functional groups in the linker group are in a protected state, or which contain a precursor of the group, as discussed below.

Thus according to a further aspect of the invention a compound of formula (1) wherein at least one of X^1, X^2, X^3 and X^4 is other than a linker group, or a metal salt thereof may be prepared by reaction of a compound of formula (2):



(2)

[wherein A^1 is $-(CH_2)_p-$ or $-(CH_2)_p N(H) (CH_2)_q-$ a least one of the groups X is a hydrogen atom and the remainder is each a group $-CH(R^1)X^1$, where R^1 is as previously defined and X^1 is a linker group] with a compound $DCH(R^2)X^2$ (where X^2 is as defined for formula (1), but is not a linker group, and D is a displaceable group, for example a halogen atom such as a bromine atom) followed, where necessary, by removal of any protecting group.

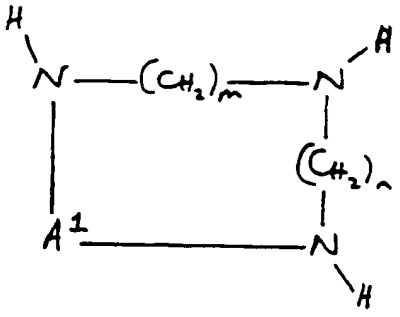
The reaction may be performed in a solvent such as water or an organic solvent such as a nitrile, e.g. acetonitrile, or an alcohol, e.g. ethanol, or an amide, e.g. dimethylformamide, in the presence of a base such as an alkali metal carbonate or hydroxide, e.g. sodium, potassium or caesium carbonate, or sodium, potassium or lithium hydroxide, at an elevated temperature e.g. the reflux temperature.

Where metal complexes of formula (1) are required (or any other suitable macrocylic intermediate described herein) these may be prepared by treating the compound with a metal salt (for example a metal halide) in an appropriate solvent for example an aqueous or non aqueous solvent, (e.g. acetonitrile, acetone, propylene carbonate, dimethylformamide or dimethylsulphoxide) at any suitable temperature from 0°C to 100°C such as 10°C to 80°C e.g. around 60°C.

A conjugate compound according to the invention may be prepared by reaction of a compound of formula (1) or a metal complex thereof with a protein, peptide or carbohydrate in a aqueous solvent, for example an inorganic buffer such as a phosphate buffer at an appropriate temperature.

Salts of compounds of formula (1) and their metal complexes may be prepare by conventional means, for example by reaction with an appropriate base or acid in a suitable aqueous solvent.

Intermediates of formula (2) may be prepared by reaction of a compound of formula (3)



(3)

with a compound $DCH(R^1)X^1$ (where X^1 is a linker group or a protected derivative thereof) in the presence of a base in a suitable solvent at an elevated temperature as just described for the preparation of compounds of formula (1). By varying the molar ratio of the compound of formula (2) and the compound $DCH(R^1)X^1$ such that the latter is increased relative to the former, (for example from around 2:1 to 1:1 and further) compounds of formula (2) containing more than $-CH(R^1)X^1$ group as just defined may be prepared.

Intermediates of formula (3) are either known compounds or may be prepared from known starting materials using methods analogous to those used for the preparation of the known compounds.

The following Examples illustrate the invention.

Example 1

(a) To a stirred solution of 1,4,7,10-tetraazacyclododecane (0.057g) in dry dimethylformamide (5ml) was added anhydrous potassium carbonate (0.05g). To this mixture at 80°C under nitrogen was added 2-bromo-6-benzamidoethyl hexanoate (0.113g) in dimethylformamide (5ml) over 2 hours. HPLC analysis revealed that after 2 days reactions was essentially complete to give, after removal of dimethylformamide a single major product [CM-300; gradient elution; t=0: A=80%, B=0%, C=20%; t=5min: A=60%, B=20%, C=20%; t=10 min: A=0%, B=80%, C=20% (with A=H_2O, B=1M ammonium acetate (pH5.6), C=CH_3CN) flow rate = 1.4ml:min^{-1}]. Retention time = 7.5min. m/e (CI) 433 (M^++1) $\delta_H(CDCl_3)$ 1.25 (3H, t, $CO_2CH_2\underline{CH_3}$), 1.45-1.79 (6H, mult, $\underline{CH_2CH_2CH_2CH_2}NH$), 2.39-3.13 (16H m.ring CH_2's) 3.32-3.50 (3H, m, $CONH\underline{CH_2}$ and $OCO\underline{CH}$), 4.14 (2H, q, CH_2O), 7.37-7.50 (4H, m, arom plus NHCO), 7.79 (2H, d+d ortho arom H).

(b) The compound prepared in part (a) was not isolated but was redissolved in dimethylformamide (5ml). To this solution was added dry potassium carbonate (0.15g) and at 80°C ethyl bromoacetate (0.165g) was added to a solution in dimethylformamide (2ml) over 15 min. Reaction was complete in 4 hours [HPLC analysis gave a major product at t=6.19 min under the conditions defined in part (a)]. After removal of dimethylformamide in vacuo the residue was chromatographed on neutral alumina (0.5% methanol/CH_2Cl_2 - 5% methanol/CH_2Cl_2) to yield as a pale oil the compound of formula (1) wherein A is $-(CH_2)_pN(R)(CH_2)_q-$, m, n, p and q is each an integer 2; R^1, R^2, R^3 and R^4 is each a group $-CO_2CH_2CH_3$; X^1, X^3 and X^4 is each a hydrogen atom; and X^2 is a group $-(CH_2)_4NHCOPh$ (wherer Ph is phenyl). m/e (DCE, ethanol) 692 (M^++1). $\delta_H(CDCl_3)$ 1.25 (12H, t+t+t, Me), 1.40-1.90 (6H, mult, $\underline{CH_2CH_2CH_2}CH_2NHCO$), 2.13-3.20 (16H, mult, ring CH_2), 3.30-3.55 (9H, mult, CH_2CO+CHCO+CH_2NHCO), 4.08-4.18 (8H, mult., OCH_2) 7.40 (3H, brd, arom H), 7.94-8.07 (3H, brd + mult., ortho CH + NHCO).

Example 2

A solution of the compound of Example 1(b) (30mg) in hydrochloric acid (6M, 10ml) was heated to reflux for 36h. After cooling, and washing with diethyl ether (3 x 3ml), the removal of solvent under high vacuum yielded the compound of formula (1) wherein A is $-(CH_2)_pN(R)(CH_2)_q-$, m, n, p and q is each an integer 2, R^1, R^2, R^3 and R^4 is each a group -

CO_2H, X^1, X^3 and X^4 is each a hydrogen atom and X^2 is a group $-(CH_2)^4NH_2$ as its tetrahydrochloride (28mg). $\partial_H(D_2O)$ 1.64 (6H, br. mult., CH_2C), 2.93-4.16 (25H, mult. br., CH_2N+ CHN), m/e (negative FAB, m-nitrobenzyl alcohol) 476 (M^-), 475 (M^--1).

Example 3

To a solution of the compound of Example 2 (9.5mg) in dry DMF (200µl) was added a solution of N-succinimidyl-3-maleimidopropiorate (14.0mg) in dry DMF (60µl), and N-methyl morpholine (40mg) yielding a slight precipitate. Addition of MilliQ water (0.003ml) dissolved the precipitate and the mixture was held at 30°C for 24h. After removal of solvent under reduced pressure, the residue was purified on reverse-phase HPLC (Spherisorb 50DS2) to yield as a colourless glass and compound of formula (1) corresponding to the compound of Example 2 except that X^2 is a group $-(CH_2)_4NHCO(CH_2)_2-$

m/e (FAB, m-nitribenzylalcohol) 628 (M'+1), 552, 493, 409. $\partial_H(D_2O)$ 6.85 (2H,s, CH=CH), 3.96-3.91 (7H, mult, CH_2N+CHN), 3.85 3.05 (20H mult. br. CH_2N+CH_2NHCO+CH_2NCO), 2.50 (2H, t, J=6.4, CH_2CONH), 1.65 (6H, mult, CH_2C). Rt =8.9 min (Spherisorb ODS2, 1.4ml min^{-1}, t=0, 95% 0.1% TFA in H_2O, 5% 0.1% TFA in CH_3CN t=20, 5% 0.1% TFA in H_2O, 95% 0.1% TFA in CH_3CN).

To a solution of the tetraacid (10µmol) in ammonium acetate buffer (90µl, pH6.0) was added 5µl[3] of an ^{90}Y solution (2µCi) and the mixture was incubated for 0.5h at 37°C. Reaction was quenched by addition of a 20 fold excess of diethylenetriamindpentaacetic acid (DTPA) and the relative amounts of 90Y complex and 90Y-DTPA determined by HPLC radiometry (AX-300 anion exchange: eluant 0.2M NH_4OAC, 10% CH_3CN). A radiolabelling yield of 77% was calculated. In the presence of a 500 fold excess of DTPA at 25°C the relative concentration of the radiolabelled complex was measured at 24, 48 and 72h and seen not to diminish (±2%).

Example 4

To a solution of 1,4,7-triazacyclononane (0.104g) in dry dimethylformamide (5ml) was added potassium carbonate (0.117g) followed by 2-bromo-6-benzamidoethyl hexanoate (0.276g) as a solution in dimethylformamide (3ml). After stirring for 50h at 50°C, the cooled solution was filtered and solvent removed under reduced pressure to give a colourless oil, m/e (DCI, ethanol) 652 (M'+1); HPLC [CM300; 2 major peaks (λmax 235nm) at 2.4 and 4.7 min with t=0: A=70%, B=10%, C=20%,; t=10min: A=0%, B=80%, C=20% (A=$H_2$0, B=1M ammonium acetate, C=CH_3CN)].

To a solution of the crude oil in dry ethanol (2ml) was added caesium carbonate (0.163g) and ethyl bromoacetate (0.083g). The mixture was stirred for 20 hours at 60°C when the solution was cooled, filtered and solvent removed to yield a pale yellow residue which was chromatographed on neutral alumina (1% methanol/CH_2Cl_2) to give as a colourless oil [Rf=0.5(2.5% methanol/CH_2Cl_2)] the compound of formula (1) wherein A is $-(CH_2)_p$, m, n and p is each an integer 2, R^1, R^2 and R^3 is each a group $-CO_2CH_2CH_3$, X^1 and X^2 is each a group $-(CH_2)_4NHCOPh$ (where Ph is phenyl) and X^3 is a hydrogen atom. m/e (DCI, ethanol) 738 (M'+1), 621, 420. δ_H($CDCl_3$ 298K) 1.24 (9H, t, CH_3, J=7.1Hz), 1.29-1.68 (12H, mult., $\underline{CH_2CH_2CH_2}CH_2NH$), 2.77-3.46 (20H, mult., CH_2N, CHN), 4.11 (6H, q + q, CH_20), 6.66 (2H, brs, NHCO), 7.42 (6H, mult., arom H), 7.79 (4H, dd, ortho CH).

Example 5

The compound of formula (1) wherein A is $-(CH_2)_p-$, m, n and p is each an integer 2, R^1, R^2 and R^3 is each a group $-CO_2CH_2CH_3$, X^1 is a group $-(CH_2)_4NHCOPh$ (where Ph is phenyl) and X^2 and X^3 is each a hydrogen atom was prepared using the methods of Example 4 except 1,4,7-triazacyclononane and 2-bromo-6-benzamidoethyl hexanoate were used in a 2:1 molar ratio. The product was purified by column chromatography on neutral alumina to yield a colourless oil, Rf=0.4 (2% methanol/CH_2Cl_2). m/e (DCI, ethanol) 563 (M'+1). δ_H ($CDCl_3$, 298K) 1.25 (1H, t + t, CH_3), 1.28-1.69 (6H, mult., $\underline{CH_2CH_2CH_2}CH_2$-NHCO), 2.76-3.02 (12H, mult., CH_2N ring), 3.22-3.54 (7H, mult., $\underline{CH_2}NHCO + C\underline{H}CO + CH_2C0$), 4.13 (6H, q, CH_20), 6.67 (1H, brs, NHCO), 7.40 (3H, mult. arom CH), 7.79 (12H, brd, ortho CH).

Example 6

N, N^1-bis(2-(N-(3-maleimidopropanoyl)-4-aminobutyl) carboxymethyl)-N"-carboxymethyl-1, 4, 7-triazacyclononane, (10mg) was prepared from the compound of Example 4 (38mg) using a similar procedure to that described for the preparation of the compound of Example 3 from the compound of Example 1.

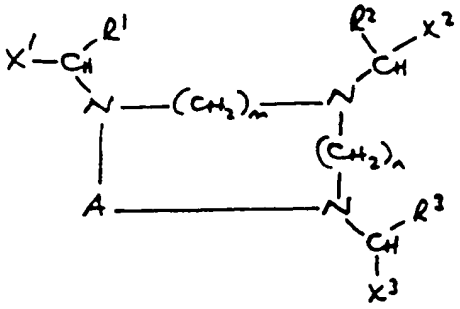
m/e (FAB, p-NBA matrix) 748(M'+1) 596; δ_H (D_2O) 6.85 (4H, S, CH=CH) 3.96 (4H, m, CH_2CO_2) 3.79 (8H, m, $C\underline{H_2}NCO$ and $C\underline{H_2}NHCO$) 3.10-3.25 (12H, m, CH_2N) 2.49 (4H, t, J6.3H_2, CH_2CONH) 1.82 (3H, m, CH_2-C) 1.46 (3H, m CH_2-C).

Example 7

N-(2-(N-(3-maleimidopropanoyl)-4-aminobutyl)carboxymethyl)-N', N''-bis(carboxymethyl0-1, 4, 7-triazacyclononane, was prepared from the compound of Example 5 using a similar procedure to that described for the preparation of the compound of Example 3 from the compound of Example 1.
m/e (FAB, p-NBA matrix) 526(M^++1) 453, 391, 307; δ_H (D_2O) 6.85 (2H, S, CH=CH) 3.95 (5H, m, CH_2CO_2) 3.79 (4H, m, CH_2NCO and CH_2NHCO) 3.00-3.50 (12H, m, CH_2N) 2.49 (2H, t, J6.2H_2, CH_2CONH) 1.69 (3H, m, CH_2-C) 1.46 (3H, m CH_2-C).

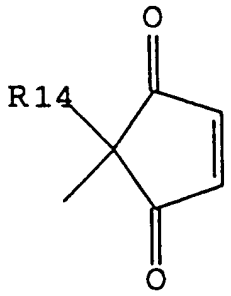
Claims

1. A compound of formula (1):



(1)

wherein
A is a group $-(CH_2)_p-$ or $-(CH_2)_p N(R)(CH_2)_q-$ where
R is a group $-CH(R^4)X^4$;
m, n, p, and q is each an integer 2;
R^1, R^2, R^3 and R^4, which may be the same or different, is each a group $-CO_2H$, $-P(R^5)O_2H$ (where R^5 is a hydrogen atom or a C_{1-6} alkyl or alkoxy group), $-PO_3H_2$ or $-CONR^6R^7$ (where R^6 and R^7, which may be the same or different is each a hydrogen atom or a C_{1-6} alkyl group); X^1, X^2, X^3 and X^4, which may be the same or different, is each a hydrogen atom or a C_{1-6} alkyl group, or a linker group of the formula -L-Z wherein L is an optionally substituted straight or branched C_{1-20} alkylene, C_{2-20} alkenylene, or C_{2-20} alkynylene chain, optionally interrupted by one or more -O- or -S- atoms or C_{5-8} cycloalkylene, C_{6-12} aromatic, C_{5-10} heteroaromatic, $N(R^8)$-, $-CON(R^8)$- or $-N-(R^8)CO-$ groups (where R^8 is a hydrogen atom or a C_{1-6} alkyl group), and Z is a halogen atom or a group selected from OH, -SH, $-NH_2$, hydrazine ($-NHNH_2$), $-N(CH_3)NH_2$, $-NHCONHNH_2$, $-NHCSNHNH_2$, or phenylhydrazine, -NCO, -NCS, $-COR^{13}$, [where R^{13} is a halogen atom or a N_3, C_{1-6} alkoxy, C_{6-12} aryloxy, imidyloxy or imidazolyloxy group], imide, a vinyl group of formula $-Het^1-C(Het^2) = CH_2$ (where Het^1 and Het^2, which may be the same or different, is each a nitrogen containing heterocyclic group, or Het^1 is a nitrogen containing heterocyclic group and Het^2 is a hydrogen atom), or a dione of formula



(where R^{14} is a C_{1-4} alkyl group); with the proviso that at least one of X^1, X^2, X^3 or X^4 is a linker group; and metal complexes and/or salts thereof.

2. A compound according to Claim 1 wherein one or two of X^1, X^2, X^3 and X^4 is a linker group and the remainder are C_{1-6} alkyl groups or hydrogen atoms.

3. A metal complex of a compound of formula (1) as defined in any of the preceding claims in which A is $-(CH_2)_pN(R)(CH_2)_q$, wherein the metal is di- or tripositive and has a coordination number 6 or greater.

4. A metal complex according to Claim 3 wherein the metal is indium, yttrium, gallium, terbium, gadolinium or scandium.

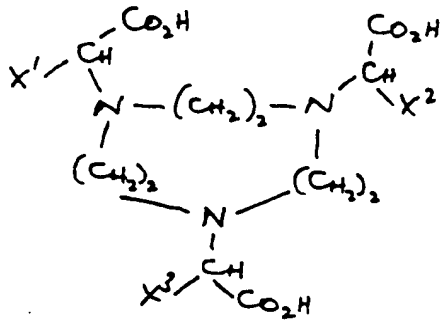
5. A metal complex according to Claim 4 wherein the metal is yttrium.

6. A metal complex of a compound according to Claim 1 or 2 in which A is $-(CH_2)_p-$, wherein the metal is di- or tripositive and has a coordination number from 2 up to 6.

7. A metal complex according to Claim 6 wherein the metal is indium, gallium, cobalt or copper.

8. A metal complex according to Claim 7 wherein the metal is indium.

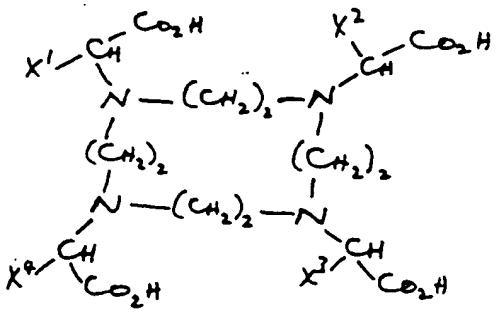
9. A compound of formula (1b) according to claim 1



(1b)

wherein one or two of X^1, X^2 or X^3 is a linker group as defined in claim 1 and the remainder are hydrogen atoms; and metal complexes and/or salts thereof.

10. A compound of formula (1d) according to claim 1

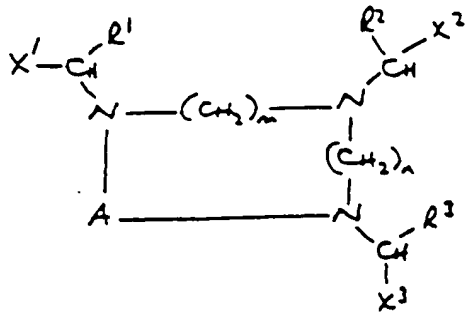


(1d)

wherein one or two of X^1, X^2, X^3 or X^4 is a linker group as defined in claim 1 and the remainder are hydrogen atoms; and metal complexes and/or salts thereof.

Patentansprüche

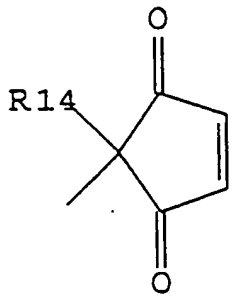
1. Verbindung der Formel (1):



(1)

worin

A eine Gruppe $-(CH_2)_p-$ oder $-(CH_2)_pN(R)(CH_2)_q-$ ist, worin R eine Gruppe $-CH(R^4)X^4$ ist;
m, n, p und q jeweils die ganze Zahl 2 sind;
R^1, R^2, R^3 und R^4, welche gleich oder verschieden sein können, jeweils eine Gruppe $-CO_2H$, $-P(R^5)O_2H$ (worin R^5 ein Wasserstoffatom oder eine C_{1-6}Alkyl- oder eine Alkoxygruppe ist), $-PO_3H_2$ oder $-CONR^6R^7$ (worin R^6 und R^7, welche gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine C_{1-6}Alkylgruppe sind), sind;
X^1, X^2, X^3 und X^4, welche gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe oder eine Verbindungsgruppe der Formel -L-Z sind, worin L eine gegebenenfalls substutierte, gerade oder verzweigte C_{1-20}Alkylen-, C_{2-20}Alkenylen- oder C_{2-20}Alkynylenkette ist, die gegebenenfalls durch ein oder mehrere -O- oder -S- Atome oder C_{5-8}Cycloalkylengruppen, aromatische C_{6-12}Gruppen, heteroaromatische C_{5-10}Gruppen, $N(R^8)$-, $-CON(R^8)$- oder $-N-(R^8)CO$-Gruppen (worin R^8 ein Wasserstoff oder eine C_{1-6}Alkylgruppe ist) unterbrochen ist, und Z ist: ein Halogenatom oder eine Gruppe, ausgewählt aus OH, -SH, $-NH_2$, Hydrazin ($-NHNH_2$), $-N(CH_3)NH_2$, $-NHCONHNH_2$, $-NHCSNHNH_2$ oder Phenylhydrazin, -NCO, -NCS, $-COR^{13}$, [worin R^{13} ein Halogenatom oder eine N_3-, C_{1-6}Alkoxy, C_{6-12}Aryloxy-, Imidyloxy- oder Imidazolyloxygruppe ist], Imid, einer Vinylgruppe der Formel $-Het^1-C(Het^2)=CH_2$ (worin Het^1 und Het^2, welche gleich oder verschieden sein können, jeweils eine Stickstoff-enthaltende heterocyclische Gruppe sind, oder Het^1 eine Stickstoff-enthaltende heterocyclische Gruppe ist und Het^2 ein Wasserstoffatom ist), oder ein Dion der Formel



(worin R^{14} eine C_{1-4}Alkylgruppe ist); mit der Maßgabe, daß mindestens eine von X^1, X^2, X^3 oder X^4 eine Verbindungsgruppe ist;
und Metallkomplexe und/oder Salze davon.

2. Verbindung nach Anspruch 1, wobei eine oder zwei von X^1, X^2, X^3 und X^4 eine Verbindungsgruppe ist bzw. sind und der Rest C_{1-6}Alkylgruppen oder Wasserstoffatome sind.

3. Metallkomplex einer Verbindung der Formel (1), wie in einem vorhergehenden Anspruch definiert, in welcher A -$(CH_2)_pN(R)(CH_2)_q$ ist, worin das Metall zweifach oder dreifach positiv ist und eine Koordinationzahl von 6 oder höher aufweist.

4. Metallkomplex nach Anspruch 3, wobei das Metall Indium, Yttrium, Gallium Terbium, Gadolinium oder Scandium ist.

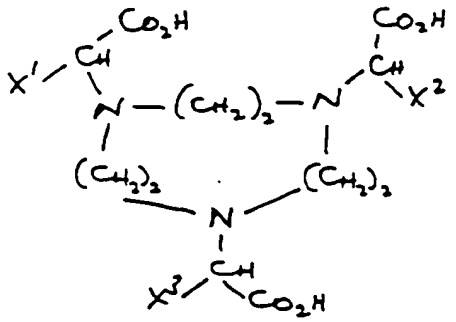
5. Metallkomplex nach Anspruch 4, wobei das Metall Yttrium ist.

6. Metallkomplex einer Verbindung nach Anspruch 1 oder 2, in welcher A -$(CH_2)_p$- ist, wobei das Metall zweifach oder dreifach positiv ist und eine Koordinationszahl von 2 bis 6 aufweist.

7. Metallkomplex nach Anspruch 6, wobei das Metall Indium Gallium, Cobalt oder Kupfer ist.

8. Metallkomplex nach Anspruch 7, wobei das Metall Indium ist.

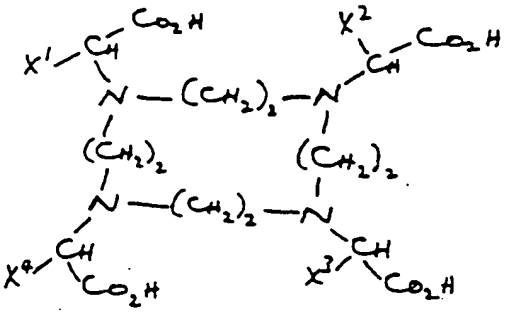
9. Verbindung der Formel (1b) nach Anspruch 1



(1b)

wobei eine oder zwei von X^1, X^2 oder X^3 eine wie in Anspruch 1 definierte Verbindungsgruppe ist bzw. sind und der Rest Wasserstoffatome sind;
und Metallkomplexe und/oder Salze davon.

10. Verbindung der Formel (1d) nach Anspruch 1

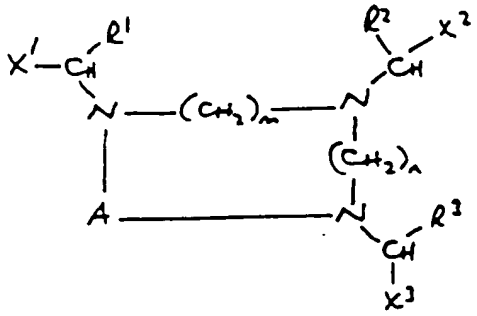


(1d)

wobei eine oder zwei von X^1, X^2, X^3 oder X^4 eine wie in Anspruch 1 definierte Verbindungsgruppe ist bzw. sind und der Rest Wasserstoffatome sind;
und Metallkomplexe und/oder Salze davon.

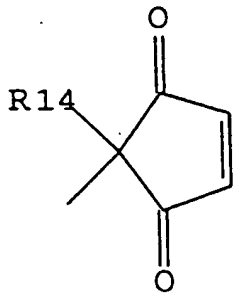
Revendications

1. Composé de formule (1):



(1)

dans laquelle
A est un groupe $-(CH_2)_p-$ ou $-(CH_2)_pN(R)(CH_2)_q-$, où
R est un groupe $-CH(R^4)X^4$;
m, n, p et q sont chacun un nombre entier égal à 2;
R^1, R^2, R^3 et R^4, qui peuvent être identiques ou différents, sont chacun un groupe $-CO_2H$, $-P(R^5)O_2H$ (dans lequel R^5 est un atome d'hydrogène ou un groupe alkyle ou alcoxy en C_1-C_6), $-PO_3H_2$ ou $-CONR^6R^7$ (où R^6 et R^7, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène ou un groupe alkyle en C_1-C_6); X^1, X^2, X^3 et X^4, qui peuvent être identiques ou différents, sont chacun un atome d'hydrogène ou un groupe alkyle en C_1-C_6, ou un groupe de liaison de formule -L-Z, dans laquelle L est une chaîne alkylène en C_1-C_{20}, alcénylène en C_2-C_{20} ou alcynylène en C_2-C_{20}, linéaire ou ramifiée, éventuellement substituée, éventuellement interrompue par un ou plusieurs atomes -O- ou -S-, ou des groupes cycloalkylène en C_5-C_8, aromatiques en C_6-C_{12}, hétéroaromatiques en C_5-C_{10}, $N(R^8)$-, $-CON(R^8)-$ ou $-N-(R^8)CO-$ (où R^8 est un atome d'hydrogène ou un groupe alkyle en C_1-C_6), et Z est un atome d'halogène ou un groupe choisi parmi OH, -SH, $-NH_2$, hydrazine ($-NHNH_2$), $-N(CH_3)NH_2$, $-NHCONHNH_2$, $-NHCSNHNH_2$ ou phénylhydrazine, -NCO, -NCS, $-COR^{13}$ [dans lequel R^{13} est un atome d'halogène ou un groupe N_3, alcoxy en C_1-C_6, aryloxy en C_6-C_{12}, imidyloxy ou imidazolyloxy], imide, un groupe vinyle de formule $-Het^1-C(Het^2)=CH_2$ (dans laquelle Het^1 et Het^2, qui peuvent être identiques ou différents, sont chacun un groupe hétérocyclique azoté, ou bien Het^1 est un groupe hétérocyclique azoté et Het^2 est un atome d'hydrogène), ou une dione de formule



(dans laquelle R^{14} est un groupe alkyle en C_1-C_4); à condition que l'un au moins des radicaux X^1, X^2, X^3 et X^4 soit un groupe de liaison; et ses sels et/ou complexes métalliques.

2. Composé selon la revendication 1, dans lequel un ou deux des radicaux X^1, X^2, X^3 et X^4 est un groupe de liaison et ceux qui restent sont des groupes alkyle en C_1-C_6 ou des atomes d'hydrogène.

3. Complexe métallique d'un composé de formule (1) telle que définie dans l'une quelconque des revendications précédentes, dans lequel A est $-(CH_2)_pN(R)(CH_2)_q-$, où le métal porte deux ou trois charges positives et possède un indice de coordination égal ou supérieur à 6.

4. Complexe métallique selon la revendication 3, dans lequel le métal est l'indium, l'yttrium, le gallium, le terbium, le gadolinium ou le scandium.

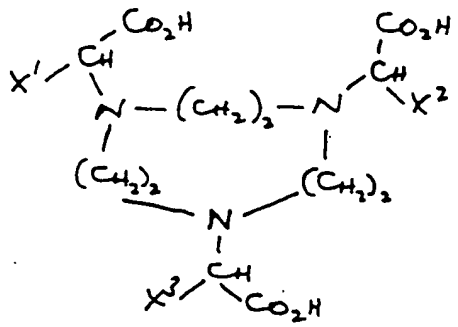
5. Complexe métallique selon la revendication 4, dans lequel le métal est l'yttrium.

6. Complexe métallique d'un composé selon la revendication 1 ou 2, dans lequel A est $-(CH_2)_p-$, où le métal porte deux ou trois charges positives et possède un indice de coordination de 2 à 6.

7. Complexe métallique selon la revendication 6, dans lequel le métal est l'indium, le gallium, le cobalt ou le cuivre.

8. Complexe métallique selon la revendication 7, dans lequel le métal est l'indium.

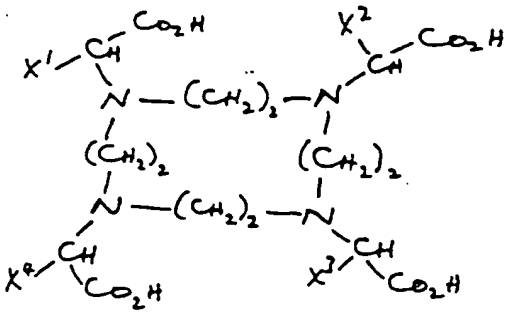
9. Composé de formule (1b) selon la revendication 1



(1b)

dans lequel un ou deux des radicaux X^1, X^2 et X^3 est un groupe de liaison tel que défini dans la revendication 1, et ceux qui restent sont des atomes d'hydrogène;
et ses sels et/ou complexes métalliques.

10. Composé de formule (1d) selon la revendication 1



(1d)

dans lequel un ou deux des radicaux X^1, X^2, X^3 et X^4 est un groupe de liaison tel que défini dans la revendication 1, et ceux qui restent sont des atomes d'hydrogène;
et ses sels et/ou complexes métalliques.